

### Claims

1. (currently amended) A heterologous fusion protein comprising a GLP-1 analog comprising a sequence selected from the group consisting of:

a) (SEQ ID NO:1)

His-Xaa<sub>8</sub>-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Glu- Gln-  
Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Gly-Gly

wherein Xaa<sub>8</sub> is selected from Gly and Val;

b) (SEQ ID NO:2)

His-Xaa<sub>8</sub>-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Glu- Gln-  
Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Lys-Asn-Gly-Gly-Gly

wherein Xaa<sub>8</sub> is selected from Gly and Val;

c) (SEQ ID NO:3)

His-Xaa<sub>8</sub>-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Glu- Gln-  
Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Gly-Pro

wherein Xaa<sub>8</sub> is selected from Gly and Val;

d) (SEQ ID NO:4)

His-Xaa<sub>8</sub>-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Glu- Gln-  
Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Lys-Asn-Gly-Gly-Pro

wherein Xaa<sub>8</sub> is selected from Gly and Val;

e) (SEQ ID NO:5)

His-Xaa<sub>8</sub>-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Glu- Gln-  
Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Gly

wherein Xaa<sub>8</sub> is selected from Gly and Val;

f) (SEQ ID NO:6)

His-Xaa<sub>8</sub>-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Glu- Gln-  
Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Lys-Asn-Gly-Gly

wherein Xaa<sub>8</sub> is selected from Gly and Val;

fused to the Fc portion of an immunoglobulin comprising the sequence of  
SEQ ID NO:7

Ala-Glu-Ser-Lys-Tyr-Gly-Pro-Pro-Cys-Pro-Pro-Cys-Pro-Ala-Pro-  
Xaa<sub>16</sub>-Xaa<sub>17</sub>-Xaa<sub>18</sub>-Gly-Gly-Pro-Ser-Val-Phe-Leu-Phe-Pro-Pro-Lys-Pro-  
Lys-Asp-Thr-Leu-Met-Ile-Ser-Arg-Thr-Pro-Glu-Val-Thr-Cys-Val-

Serial No. 10/558,627  
Docket No. X-15984

Val-Val-Asp-Val-Ser-Gln-Glu-Asp-Pro-Glu-Val-Gln-Phe-Asn-Trp-  
Tyr-Val-Asp-Gly-Val-Glu-Val-His-Asn-Ala-Lys-Thr-Lys-Pro-Arg-  
Glu-Glu-Gln-Phe-Xaa<sub>80</sub>-Ser-Thr-Tyr-Arg-Val-Val-Ser-Val-Leu-Thr-  
Val-Leu-His-Gln-Asp-Trp-Leu-Asn-Gly-Lys-Glu-Tyr-Lys-Cys-Lys-  
Val-Ser-Asn-Lys-Gly-Leu-Pro-Ser-Ser-Ile-Glu-Lys-Thr-Ile-Ser-  
Lys-Ala-Lys-Gly-Gln-Pro-Arg-Glu-Pro-Gln-Val-Tyr-Thr-Leu-Pro-  
Pro-Ser-Gln-Glu-Glu-Met-Thr-Lys-Asn-Gln-Val-Ser-Leu-Thr-Cys-  
Leu-Val-Lys-Gly-Phe-Tyr-Pro-Ser-Asp-Ile-Ala-Val-Glu-Trp-Glu-  
Ser-Asn-Gly-Gln-Pro-Glu-Asn-Asn-Tyr-Lys-Thr-Thr-Pro-Pro-Val-  
Leu-Asp-Ser-Asp-Gly-Ser-Phe-Phe-Leu-Tyr-Ser-Arg-Leu-Thr-Val-  
Asp-Lys-Ser-Arg-Trp-Gln-Glu-Gly-Asn-Val-Phe-Ser-Cys-Ser-Val-  
Met-His-Glu-Ala-Leu-His-Asn-His-Tyr-Thr-Gln-Lys-Ser-Leu-Ser-  
Leu-Ser-Leu-Gly-Xaa<sub>230</sub> (SEQ ID NO:7)

wherein:

Xaa at position 16 is ~~Pro~~ or Glu;

Xaa at position 17 is ~~Phe, Val~~, or Ala;

Xaa at position 18 is ~~Leu, Glu~~, or Ala;

Xaa at position 80 is ~~Asn~~ or Ala; and

Xaa at position 230 is Lys or is absent;

and further comprising a peptide linker of SEQ ID NO:8

Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser

wherein the peptide linker is between the C-terminal glycine residue of the GLP-1 analog and the N-terminal alanine of the Fc portion.

2. (withdrawn) The heterologous fusion protein of Claim 1 wherein the C-terminal glycine residue of the GLP-1 analog is fused to the N-terminal alanine residue of the Fc portion via a peptide linker comprising a sequence selected from the group consisting of:
  - a) Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser (SEQ ID NO:8);
  - b) Gly-Ser-Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser (SEQ ID NO:19); and

Serial No. 10/558,627

Docket No. X-15984

- c) Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser (SEQ ID NO:21).
3. (withdrawn) The heterologous fusion protein of Claim 2 wherein the linker comprises the sequence of SEQ ID NO:8.
  4. (withdrawn) The heterologous fusion protein of any one of Claims 1 to 3 wherein Xaa at position 8 of the GLP-1 analog is Gly.
  5. (withdrawn) The heterologous fusion protein of any one of Claims 1 to 3 wherein Xaa at position 8 of the GLP-1 analog is Val.
  6. (withdrawn) The heterologous fusion protein of any one of Claims 1 to 3 wherein the GLP-1 analog comprises the sequence of SEQ ID NO:1.
  7. (withdrawn) A heterologous fusion protein selected from the group consisting of: a) Gly<sup>8</sup>-Glu<sup>22</sup>-Gly<sup>36</sup>-GLP-1(7-37)-1L-IgG4 (S228P); b) Gly<sup>8</sup>-Glu<sup>22</sup>-Gly<sup>36</sup>-GLP-1(7-37)-1L-IgG4 (S228P, F234A, L235A); c) Gly<sup>8</sup>-Glu<sup>22</sup>-Gly<sup>36</sup>-GLP-1(7-37)-1L-IgG4 (S228P, N297A); d) Gly<sup>8</sup>-Glu<sup>22</sup>-Gly<sup>36</sup>-GLP-1(7-37)-1L-IgG4 (S228P, F234A, L235A, N297A); e) Gly<sup>8</sup>-Glu<sup>22</sup>-Gly<sup>36</sup>-GLP-1(7-37)-1.5L-IgG4 (S228P); f) Gly<sup>8</sup>-Glu<sup>22</sup>-Gly<sup>36</sup>-GLP-1(7-37)-1.5L-IgG4 (S228P, F234A, L235A); g) Gly<sup>8</sup>-Glu<sup>22</sup>-Gly<sup>36</sup>-GLP-1(7-37)-1.5L-IgG4 (S228P, N297A); h) Gly<sup>8</sup>-Glu<sup>22</sup>-Gly<sup>36</sup>-GLP-1(7-37)-1.5L-IgG4 (S228P, F234A, L235A, N297A); i) Gly<sup>8</sup>-Glu<sup>22</sup>-Gly<sup>36</sup>-GLP-1(7-37)-2L-IgG4 (S228P); j) Gly<sup>8</sup>-Glu<sup>22</sup>-Gly<sup>36</sup>-GLP-1(7-37)-2L-IgG4 (S228P, F234A, L235A); k) Gly<sup>8</sup>-Glu<sup>22</sup>-Gly<sup>36</sup>-GLP-1(7-37)-2L-IgG4 (S228P, N297A); l) Gly<sup>8</sup>-Glu<sup>22</sup>-Gly<sup>36</sup>-GLP-1(7-37)-2L-IgG4 (S228P, F234A, L235A, N297A); and the des-K forms thereof.
  8. (withdrawn) A heterologous fusion protein selected from the group consisting of: a) Val<sup>8</sup>-Glu<sup>22</sup>-Gly<sup>36</sup>-GLP-1(7-37)-1L-IgG4 (S228P); b) Val<sup>8</sup>-Glu<sup>22</sup>-Gly<sup>36</sup>-GLP-1(7-37)-1L-IgG4 (S228P, F234A, L235A); c) Val<sup>8</sup>-Glu<sup>22</sup>-Gly<sup>36</sup>-GLP-1(7-37)-1L-IgG4 (S228P, N297A); d) Val<sup>8</sup>-Glu<sup>22</sup>-Gly<sup>36</sup>-GLP-1(7-37)-1L-IgG4 (S228P, F234A, L235A, N297A); e) Val<sup>8</sup>-Glu<sup>22</sup>-Gly<sup>36</sup>-GLP-1(7-37)-1.5L-IgG4 (S228P); f) Val<sup>8</sup>-Glu<sup>22</sup>-Gly<sup>36</sup>-GLP-1(7-37)-1.5L-IgG4 (S228P, F234A, L235A); g) Val<sup>8</sup>-Glu<sup>22</sup>-Gly<sup>36</sup>-GLP-1(7-37)-1.5L-IgG4 (S228P, N297A); h) Val<sup>8</sup>-Glu<sup>22</sup>-Gly<sup>36</sup>-GLP-1(7-37)-1.5L-IgG4 (S228P, F234A, L235A, N297A); i) Val<sup>8</sup>-Glu<sup>22</sup>-Gly<sup>36</sup>-GLP-1(7-37)-2L-IgG4 (S228P); j) Val<sup>8</sup>-Glu<sup>22</sup>-Gly<sup>36</sup>-GLP-1(7-37)-2L-IgG4 (S228P, F234A, L235A); k) Val<sup>8</sup>-Glu<sup>22</sup>-Gly<sup>36</sup>-GLP-1(7-37)-2L-IgG4 (S228P, N297A); l) Val<sup>8</sup>-Glu<sup>22</sup>-Gly<sup>36</sup>-GLP-1(7-37)-2L-IgG4 (S228P, F234A, L235A, N297A); and the des-K forms thereof.
  - 9.-15. (cancelled)

Serial No. 10/558,627

Docket No. X-15984

16. (withdrawn) A method of treating a patient with non-insulin dependent diabetes mellitus comprising the administration of a therapeutically effective amount of the heterologous fusion protein of any one of Claims 1 to 8.
17. (withdrawn) A method of inducing weight loss in an overweight patient comprising the administrations of a therapeutically effective amount of the heterologous fusion protein of any one of Claims 1 to 8.
18. (withdrawn) The method of Claim 16 or 17 wherein the heterologous fusion protein is administered at a dose between about 0.05 mg/kg to 0.5 mg/kg body weight.
19. (withdrawn) The method of Claim 16 or 17 wherein the heterologous fusion protein is administered once a week.
- 20.-24. (cancelled)
25. (withdrawn) A method of treating a patient with non-insulin dependent diabetes mellitus comprising the administration of a therapeutically effective amount of the heterologous fusion protein of any one of Claims 1 to 8, wherein the fusion protein stimulates insulin secretion, inhibits glucagon secretion, inhibits gastric emptying, inhibits gastric or intestinal motility, or induces weight loss.
26. (new) A heterologous fusion protein comprising a GLP-1 analog of (SEQ ID NO:1)  
His-Xaa<sub>8</sub>-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Glu- Gln-  
Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Gly-Gly  
wherein Xaa<sub>8</sub> is Gly;  
fused to the Fc portion of an immunoglobulin of SEQ ID NO:7  
Ala-Glu-Ser-Lys-Tyr-Gly-Pro-Pro-Cys-Pro-Pro-Cys-Pro-Ala-Pro-  
Xaa<sub>16</sub>-Xaa<sub>17</sub>-Xaa<sub>18</sub>-Gly-Gly-Pro-Ser-Val-Phe-Leu-Phe-Pro-Pro-Lys-Pro-  
Lys-Asp-Thr-Leu-Met-Ile-Ser-Arg-Thr-Pro-Glu-Val-Thr-Cys-Val-  
Val-Val-Asp-Val-Ser-Gln-Glu-Asp-Pro-Glu-Val-Gln-Phe-Asn-Trp-  
Tyr-Val-Asp-Gly-Val-Glu-Val-His-Asn-Ala-Lys-Thr-Lys-Pro-Arg-  
Glu-Glu-Gln-Phe-Xaa<sub>80</sub>-Ser-Thr-Tyr-Arg-Val-Val-Ser-Val-Leu-Thr-  
Val-Leu-His-Gln-Asp-Trp-Leu-Asn-Gly-Lys-Glu-Tyr-Lys-Cys-Lys-  
Val-Ser-Asn-Lys-Gly-Leu-Pro-Ser-Ser-Ile-Glu-Lys-Thr-Ile-Ser-  
Lys-Ala-Lys-Gly-Gln-Pro-Arg-Glu-Pro-Gln-Val-Tyr-Thr-Leu-Pro-  
Pro-Ser-Gln-Glu-Glu-Met-Thr-Lys-Asn-Gln-Val-Ser-Leu-Thr-Cys-  
Leu-Val-Lys-Gly-Phe-Tyr-Pro-Ser-Asp-Ile-Ala-Val-Glu-Trp-Glu-

Serial No. 10/558,627

Docket No. X-15984

Ser-Asn-Gly-Gln-Pro-Glu-Asn-Asn-Tyr-Lys-Thr-Thr-Pro-Pro-Val-  
Leu-Asp-Ser-Asp-Gly-Ser-Phe-Phe-Leu-Tyr-Ser-Arg-Leu-Thr-Val-  
Asp-Lys-Ser-Arg-Trp-Gln-Glu-Gly-Asn-Val-Phe-Ser-Cys-Ser-Val-  
Met-His-Glu-Ala-Leu-His-Asn-His-Tyr-Thr-Gln-Lys-Ser-Leu-Ser-  
Leu-Ser-Leu-Gly-Xaa<sub>230</sub>

wherein:

Xaa at position 16 is Glu;

Xaa at position 17 is Ala;

Xaa at position 18 is Ala;

Xaa at position 80 is Asn; and

Xaa at position 230 is absent;

and further comprising a peptide linker of SEQ ID NO:8

Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser

wherein the peptide linker is between the C-terminal glycine residue of the  
GLP-1 analog and the N-terminal alanine of the Fc portion.